INCREASING THE SOLUBILITY OF A POOR SOLUBLE API - MILK THISTLE DRY EXTRACT (SILYMARIN)

V. Dilova, Y. Stoianova

Department of Quality Management, Medica AD, BULGARIA, vdilova@medica.bg
Department of Quality Control, Medica AD, BULGARIA

Abstract: The active substance used in this study is a Milk thistle dry extract, refined and standardized (equiv. to 45 mg/90 mg Silymarin as Silibinin). The main problem with milk thistle extract (silymarin) is its poor oral bioavailability, which is attributable to its low water solubility and low permeability as well as degradation in the gastrointestinal tract. The purpose of this work was to evaluate and compare the effect of some surfactants and various sugars like lactose, sorbitol and mannitol as carriers for improvements of solubility and/or dissolution of poor aqueous soluble drug, milk thistle extract (Silymarin) from formulated capsules. The formulation containing combination of Sodium lauryl sulfate, Polysorbate 80 as solubilizers and mannitol as a diluent exhibits best rheologic characteristics and highest dissolution rate of the Milk thistle dry extract (Silymarin).

Key Words: Milk thistle dry extract, hard capsules, Sodium lauryl sulfate, Polysorbate 80, mannitol.

Introduction

About 90% of all compounds in today’s pharmaceutical drug delivery pipelines are reported to be poorly soluble in water [4]. This poses enormous problems for the industry: for an API cannot reach its molecular target in the body if the drug remains undissolved in the gastrointestinal tract (GIT). Therefore poor solubility is a critical factor if the molecule is to survive the pharmaceutical development process. Solubilization technologies by increasing solubility of such drugs are more important to the pharmaceutical industry to prepare effective and marketable drugs from API that would be useless [5].

Silymarin, extracted from the seeds of milk thistle (Silibum marianum Gaertn.) is a mixture of flavonolignans including silybin, silychristin, isosilybin, silydianin, taxifolin, and various derivatives of these components [3]. Silymarin as well as silibinin, the main active component comprising 40% to 65% of the total milk thistle extract weight EurPh and is used clinically as a hepatoprotector to treat liver injuries and chronic hepatitis. However, the main problem with milk thistle extract (silymarin) is its poor oral bioavailability, which is attributable to its low water solubility (0.04 mg/mL) of silymarin [2; 9] and low permeability as well as degradation in the gastrointestinal tract [1].

Therefore, it appears quite important to improve the solubility and/or the permeability of milk thistle extract (silymarin as silibinin) to achieve higher oral bioavailability.

A number of approaches for increasing the oral bioavailability of milk thistle extract (silymarin) have been extensively studied, including solubilization, cosolvency, complexation with β-cyclodextrins and solid dispersion [7].

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic [8].

When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles. The presence of surfactants may lower the surface tension and increase the solubility of the drug.

The purpose of this work was to evaluate and compare the effect of some surfactants and various sugars like lactose, sorbitol and mannitol as carriers for improvements of solubility and/or dissolution of poor aqueous soluble drug, milk thistle extract (Silymarin) from formulated capsules.
Materials and Methods

Materials
Milk thistle dry extract, refined and standardised (EurPh); mannitol, sodium starch glycolate; croscarmellose sodium; pregelatinized starch; polyvinylpyrrolidone; Silica, colloidal anhydrous, Sodium lauryl sulfate (NaLSO₄), Polysorbate 80, hydroxypropylmethylcellulose; hydroxypropylcellulose; microcrystalline cellulose; magnesium stearate; all excipients meet the requirements of Ph. Eur. 8.

Methods

Preparation of hard capsules
All samples of hard capsules containing 53% API (Milk thistle dry extract, refined and standardized, corresponding to 58% Silymarin, calculated as silybinin for dried extract) (equiv. to 45mg/90 mg Silymarin as Silibinin) were prepared by conventional wet granulation method.

The series of capsules (S1 – S8) were formulated with different surfactants in concentration from 1,5 to 2,0% individually or in combination respectively and mannitol, sorbitol and lactose monohydrate as sugars in concentration of 28% respectively. All the binders were used in the form of aqueous solution or colloidal solutions of suitable strength and the pregelatinized starch and croscarmellose sodium as disintegrants in concentration of 10 and 1,5 % respectively.

Capacule filling machine (Zanazi) was used to filling the hard capsules at a fixed weight.

Disintegration time studies
Disintegration time in distilled water was determined by using Erweka Tablet Disintegration Test Machine, Eur. Ph.

Analysis of API
The amount of drug in the investigated samples was determined by HPLC [USP]. The method was validated by determination of the following operational characteristics: linearity, range, precision, accuracy, limit of detection and limit of quantitation.

Dissolution testing
The dissolution rate of API from hard capsules was studied in 900 ml of phosphate buffer containing 2% sodium lauryl sulfate (pH 7,5) using USP. Disso- lution Rate Test Apparatus (Model Erweka 6DT) with paddle, a velocity 120±2 rpm and a temperature of 37±0,50 C were used in each test. Samples of dissolution medium were withdrawn through a filter at different time intervals, suitable diluted and assed for API of test solution and of reference solution.

Test to test the significance of the observed difference due to various surfactants binders and sugars.

Bulk density and tapped density according the methods described in EurPh.

Results and discussions
The formulation of Milk thistle dry extract for effective oral administration has been prevented by the unique physical and chemical properties of the API, particularly its low water solubility and factors associated with low bulk density and low compressibility.

The results of the comparative investigation on the physicomechanical properties of granules for hard gelatin capsules obtained by wet granulation are presented in Table 1.

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The results of the comparative investigation on the physicomechanical properties of granules for hard gelatin capsules obtained by wet granulation are presented in Table 1.

Table 1. Influence of different solubilizers and sugars on some basic rheologic characteristics of granules obtained by wet granulation.

<table>
<thead>
<tr>
<th>Test</th>
<th>NaLSO₄ 1,5/2% Lactose-28%</th>
<th>Polysorbate 80 1,5/2% Lactose-28%</th>
<th>NaLSO₄ 1,5% Polysorbate-1,5% Mannitol - 28%</th>
<th>NaLSO₄ 1,5% Polysorbate-2,0% Mannitol - 28%</th>
<th>NaLSO₄ 1,5% Polysorbate-1,5% Lactose-28%</th>
<th>NaLSO₄ 1,5% Polysorbate-1,5% Sorbitol - 28%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk density (g/ml)</td>
<td>2,3</td>
<td>2,3</td>
<td>2,2</td>
<td>2,2</td>
<td>2,2</td>
<td>2,5</td>
</tr>
<tr>
<td>Tapped density (g/ml)</td>
<td>1,6</td>
<td>1,6</td>
<td>1,7</td>
<td>1,7</td>
<td>1,6</td>
<td>1,8</td>
</tr>
<tr>
<td>Angle of repose (degrees)</td>
<td>34</td>
<td>37</td>
<td>31</td>
<td>30</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Hausner Ratio</td>
<td>1,43</td>
<td>1,43</td>
<td>1,29</td>
<td>1,29</td>
<td>1,37</td>
<td>1,39</td>
</tr>
</tbody>
</table>
The formulation containing NaLSO₄ (1.5%), Polysorbate 80 (1.5% or 2.0%) and mannitol (28%) shows the best results regarding density and other physical and mechanical parameters. One of the basic rheological parameter the angle of repose for all formulations shows values in a range from 29 to 37 which indicate good flow characteristics of the granulation mixtures for filling hard gelatin capsules.

Fig.1 present the results of the in vitro studies of the dissolution rate of Milk thistle dry extract (Silymarin as silibinin) from hard gelatin capsules containing different solubilizers and sugars.

- NaLSO₄ - 1.5%, Lactose - 28%
- NaLSO₄ - 2.0%, Lactose - 28%
- Polysorbate 80 - 1.5%, Lactose - 28%
- Polysorbate 80 - 2.0%, Lactose - 28%
- NaLSO₄ - 1.5%, Polysorbate - 1.5%, Mannitol - 28%
- NaLSO₄ - 1.5%, Polysorbate - 2.0%, Mannitol - 28%
- NaLSO₄ - 1.5%, Polysorbate - 1.5%, Sorbitol - 28%
- NaLSO₄ - 1.5%, Polysorbate - 1.5%, Lactose - 28%
- Polysorbate 80 - 1.5%, Lactose - 28%
- Polysorbate 80 - 2.0%, Lactose - 28%

Fig.1 shows that similar dissolution profiles are obtained for the formulations containing NaLSO₄ with HLR 40 or Polysorbate 80 with HLR 15 (1.5 or 2.0%) individually as a solubilizer and lactose monohydrate as a sugar. The integration of both solubilizers in combination results in increased solubility of the drug probably due to properties of the surfactants - NaLSO₄, as a wetting agent (HLR 40) and Polysorbate 80 (HLR 15) as a solubilizing agent for poorly soluble active constituents. Surfactant adsorption onto hydrophobic drug particles below the critical micelle concentration can aid of the particle and consequently increase the rate of solution of particulate agglomerates [10]. Surfactants may be incorporated into solid dosage forms so that their solubilizing action comes into play as the disintegration process starts and water penetration improves.

A drug release of about 60% is observed within 45 min, which means that adding NaLSO₄ or Polysorbate 80 in different concentrations (1.5; 2.0%) to the granule mixture as a solubilizers does not lead to a significant increase in the dissolution rate of the Milk thistle dry extract (Silymarin) while adding both solubilizers in combination from 1.5 to 2.0% leads to an increase in the dissolution rate of the API up to 73% (S8).

The enhancement of dissolution is mainly attributed to increased surface area of drug exposed to large carrier molecules, increased wettability, and accordingly solubility due to polar effect of sugars containing polar groups [6].

This also may be attributed to the higher hydrophilic sugar carriers, which can reduce the interfacial tension between the poorly aqueous soluble drug and the dissolution medium. In case of Milk thistle dry extract (Silymarin), the order sugar carriers for increasing dissolution in phosphate buffer (pH = 7.5) was lactose < sorbitol ≤ mannitol (S5; S7; S8) and this observation is well correlated with the results of dissolution rate from 73% for formulation with lactose and up to 84% for the formulation with mannitol (S6) which is close to the dissolution characteristic of the reference.

**Conclusion**

The different kinds of surfactants influence the rheological characteristics of the granulated mixtures to a different grade (Polysorbate 80 ≈ Sodium lauryl sulfate < Sodium lauryl sulfate + Polysorbate 80).

The formulation containing combination of Sodium lauryl sulfate, Polysorbate 80 as solubilizers and mannitol as a diluent exhibits best rheologic characteristics and highest dissolution rate of the Milk thistle dry extract (Silymarin as silibinin).

**References**

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Corresponding author
Valia Dilova
MEDICA AD
John Paul II sq., Business center "Bulgaria 2000", fl.3
1164 Sofia
e-mail: vdilova@medica